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| 10/723,354 | 11/25/2003 | Patrick L. Iversen | 50450-8311.US03 | 8250 |
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| King & Spalding LLP P.O. Box 889 Belmont, CA 94002-0889 | | | EXAMINER EPPS FORD, JANET L | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|---------------------------------------|--|--|
| Office Action Summary | Application No. 10/723,354 | Applicant(s) IVERSEN, PATRICK L. | |
| | Examiner Janet L. Epps-Ford | Art Unit 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8-25-08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 31-47 are presently pending in the instant application.

Response to Amendment/Arguments

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 31-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claims 31-39 recite the phrase "a method of improving the pharmacokinetics of a drug..." The term "improving" in this claim is a relative term which renders the claim indefinite. The term "improving" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.
6. Claims 40-47 recites a method of inhibiting the expression of a drug-metabolizing mammalian cytochrome p450 enzyme selected from the group consisting of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A2 and CYP3A4 enzymes in a subject, wherein said method comprising the administration of a morpholino antisense oligomer that hybridizes to "a target RNA molecule encoding **a** drug-metabolizing mammalian cytochrome p450 enzyme." This method is vague and

indefinite since the scope of the claim encompasses wherein any generic drug-metabolizing mammalian cytochrome p450 enzyme is targeted by an antisense oligomer, however the scope of the claim is limited to wherein the mammalian cytochrome p450 is selected from the group consisting of: CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A2 and CYP3A4 enzymes. Scope of the instant claims are vague and indefinite to the extent that it is unclear how the specifically recited cytochrome p450 enzymes of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A2 and CYP3A4 can be specifically inhibited in a subject when the scope of the claimed methods encompass wherein any generic antisense morpholino oligomer targeting a cytochrome p450 enzyme is administered to a subject.

7. The rejection of claims 31-47 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (New Matter), withdrawn in response to Applicant's amendment, however the following rejection under 35 USC 112, 1st paragraph is maintained for the reasons of record.

8. Claims 31-35, 39-43 and 47 stand rejected, and claims 36-38, and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

9. Applicant's arguments with respect to claims 31-35, 39-43 and 47 have been considered but are moot in view of the new ground(s) of rejection.

10. Instant claims 31-39 have been amended to recite (see last three lines of claim 31) "wherein the antisense oligomer blocks expression of the mammalian cytochrome p450 enzyme *by hybridizing to a target RNA molecule which encodes the enzyme.*" According to the specification as filed (see published patent application), see ¶[0028], the term "hybridize" may encompass wherein antisense oligomer has exact sequence complementarity or "near complementarity." See the following reproduction of ¶ [0028]: "[T]he terms "antisense oligonucleotide" and "antisense oligomer" are used interchangeably and refer to an oligomer having a sequence of nucleotide bases and a subunit-to-subunit backbone that allows the antisense oligomer to **hybridize** to a target sequence in an RNA by Watson-Crick base pairing, to form an RNA:oligomer heteroduplex within the target sequence. The oligomer may have **exact** sequence complementarity to the target sequence or **near** complementarity." Therefore the scope of the instant claims encompasses wherein, although the name of the target is defined and the nucleotide structure of the target sequence is undefined (i.e. there is no SEQ ID NO: which sets forth the nucleotide sequence) in the specification as filed, the antisense morpholino oligomers encompassed by the instant claims may be fully complementary, or partially complementary to the undefined target. It is noted that instant claims 40-47 also recite wherein the antisense morpholino oligomer "hybridizes" to the target RNA, therefore the above interpretation of the genus of antisense oligomers encompassed by claims 31-39 applies to claims 40-47 as well.

11. Secondly, the scope of amended claims 40-47 comprises the administration of antisense morpholino oligomers that hybridize to "a target RNA molecule encoding **a** drug-metabolizing mammalian cytochrome p450 enzyme." Therefore the scope of the antisense morpholino oligomers encompassed by this claim reads on those targeting RNA molecules encoding CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4, but also those antisense oligomers targeting all other forms of mammalian cytochrome p450 enzymes. Moreover, the scope of the antisense oligomers encompassed by claims 40-47 reads on the administration of antisense oligomers targeting cytochrome P450 enzymes isolated from any mammal, and wherein the scope of the enzymes encompasses all other allelic and polymorphic variants of the recited mammalian cytochrome P450 enzymes. Additionally, claims 40-47 are not limited to a mammalian subject.

12. Thirdly, the breadth of the claims comprises a method wherein the pharmacokinetics of any drug metabolized by CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4 is "improved", wherein the improvement is associated with the co-administration of said drug with a morpholino antisense oligomer that blocks the expression of mammalian cytochrome p450 enzyme. Note that the exact nature of the term "improving" as recited in the instant claims are vague and indefinite since the level or range of improvement of all the various parameters associated with the pharmacokinetics of these drug may vary depending on the class of drug administered, and dependent on the class of mammal the drug is administered to.

Other than the antisense oligonucleotides targeting CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2D6, CYP2E1, CYP3A2, and CYP3A4, as defined by SEQ ID NO: 1-15, Applicants have not shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. No guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed properties, since it is unknown what properties, structural or otherwise, that the antisense oligonucleotides of the present invention must possess for it to improve the pharmacokinetics of a drug in any and all mammalian subjects.

Although the prior art may teach algorithms for designing antisense oligonucleotides targeting a given defined nucleotide target sequence, the instant claims do not define the nucleotide structure of the target RNA molecule which encode the target enzymes. Moreover, the scope of the claims encompasses wherein the antisense oligomer may have "near complementarity," i.e. wherein the antisense oligomer has only a partial nucleotide structure that is defined by the sequence set forth by the target RNA, if the sequence of the target is known. Due to the variability associated with the full scope of antisense oligomers encompassed by the instant claims, further experimentation would be necessary to determine which oligomers having "near complementarity" to the target possess the function recited in the instant claims. Apart from further experimentation, no guidance is given in the specification as

filed that would allow one of skill in the art to predict the full scope of antisense morpholino oligomer compositions encompassed by the instant claims, since it is unknown what relevant identifying characteristics are sufficient to produce antisense morpholino oligomers according to the present invention which function to improve the pharmacokinetics of a drug in any and all mammalian subjects, or non-mammalian subjects (see claims 40-47). Although the instant claims are directed to a method, it is noted that the claimed methods require the use of a broad genus of compounds that are not sufficiently described in the specification as filed.

13. Claims 31-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cytochrome P450 antisense comprising the administration of the morpholino antisense oligomers targeting RNA molecules encoding CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, wherein said antisense oligomers are *fully complementary* to the target RNA encoding these enzymes, or compositions comprising said antisense oligomers, does not reasonably provide enablement for practicing the claimed invention comprising the use of antisense morpholino oligomers targeting any other mammalian cytochrome P450 or further wherein said antisense morpholino oligomers possess "near complementarity" to the target RNA encoding the mammalian cytochrome p450. Moreover, although the specification is enabled for inhibiting the metabolism of drugs that are metabolized by CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, comprising the co-administration of morpholino antisense targeting these enzymes, does not provide enablement for

improving all aspects of the pharmacokinetics of drugs metabolized by the recited cytochrome p450 enzymes in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

14. Applicant's arguments filed 7/15/08 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that the amendment of 7/15/08, which currently claims essentially in accordance with the scope of enablement defined by the Examiner in the prior Office Action.

15. Contrary to Applicant's assertion, and in response to Applicant's amendment, the claims remain rejected for the following reasons. Although the specification demonstrates the efficacy of the antisense oligonucleotides according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47 that target CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4, in the working examples, no guidance or working examples are disclosed that would allow a skilled artisan to use antisense oligonucleotides having only *partial complementarity* (i.e. which hybridize as defined in the specification as filed See ¶ [0028] of the specification as filed) to the target RNA encoding a mammalian cytochrome p450.

16. Furthermore, the scope of the instant claims encompasses antisense oligomers which *hybridize* to a target RNA. The specification as filed does not teach the skilled artisan to administer antisense oligomers targeting any generic form of cytochrome p450, and result in the inhibition of the specific enzymes of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4,

either *in vitro* or *in vivo*. Note that the scope of claims 40-47 recites the inhibition of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4 cytochrome p450 enzymes. However, the only active step in the method of claims 40-47 comprises the administration of a generic antisense oligomer which “hybridizes to a target RNA molecule encoding a drug-metabolizing mammalian cytochrome p450 enzyme.”

As stated in the prior Office Action, Applicant's own specification support the examiner's assertion of unpredictability in regards to both the design of effective antisense and their use to inhibit cytochrome p450 expression. For example, not that the specification demonstrates that several antisense oligos were ineffective in inhibiting cytochrome P450 expression, for example oligos according to SEQ ID NO: 16-17 (see Table 6, and pages 29-30), 21-22 (see page 33, lines 9-11) and 37-38 (see page 28, lines 1-4) exemplify this point. Although these antisense oligomers were designed having a sequence complementary to a mammalian cytochrome p450, they did not produce any significant inhibition of the target enzyme.

The instant claims stand rejected for the reasons of record, and those reasons set forth above.

Double Patenting

17. The rejection of Claims 31-47 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of issued US Patent No. 6,686,338, is withdrawn in response to Applicant's filing of a Terminal Disclaimer of the issued US Patent.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner, Art Unit 1633

JLE